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Detailed Report

(Name of invention)
biological sample optical scanning device

Abstract
(Object)

This invention offers a an optical scanning device for biological samples which can perform analysis work effectively by reducing scanning time remarkably. It offers a an optical scanning device for biological samples with excellent sensitivity to fluorescent light from samples marked with a fluorescent substance.

(Solution)

This optical scanning device for biological samples 1 uses light to scan the sample chip 15 where many biological samples have been arranged, and the biological sample marked with a fluorescent substance is specified. It makes a round-trip of the sample base 13. Light from a light source which passes through the hollow center of an electric motor is directed in the radial direction and up and down by a pair of opposing mirrors kept at a 45 degree angle, and it irradiates the sample chip on the base. Light from the fluorescent substance generated by light from an objective lens is received by a light-receiving part through the hollow center of the motor, and an electric signal is output.

Sphere of the patent application

(Claim 1)

Claim 1 is concerning an optical scanning device for biological samples which has the following characteristics: An optical scanning device for biological samples 1 scans a sample chip multiple times to locate biological samples that have been marked with a fluorescent substance. The optical scanning device for biological samples in this invention consists of the following: a sample base which makes a roundtrip on the main frame holds the sample chip, a controllable drive mechanism which moves the sample base, an electric motor with a hollow center that rotates around an axis which is perpendicular to the surface of the sample base, a rotation ting arm positioned on the sample base side, a pair of opposing mirrors set up at a 45 degree angle in the radial gap which is perpendicular to the axis of rotation, an object lens set up on the optical axis of one of the mirrors positioned at the end of the arm , a light source with a predetermined beam diameter which illuminates the sample base along the axis of rotation through the pair of mirrors and objective lens, a light-receiving part which receives light from the fluorescent substance generated when the substance is illuminated through the objective lens and the pair of mirrors through the hollow center of rotation. This receiver also outputs electric signals. This optical scanning device for biological samples can detect biological samples marked with a fluorescent substance by scanning the sample chip in an arc on the sample base which moves in a straight line.

(Claim 2)

In claim 1, it is concerning an optical scanning device for biological samples where the light source and light-receiving part are perpendicular to the axis of rotation. A semi transparent mirror is set up at the intersection of the optical axis of the light receiving part and optical axis of the light source.

(Claim 3)

In claim 1, it is concerning an optical scanning device for biological samples where the light source consists of a laser with a wavelength which will excite the fluorescent substance.

Detailed explanation of invention

[0001]

(Technical field that this invention belongs to)

This invention is concerning an optical scanning device for biological samples which detects a biological sample marked with a fluorescent substance such as a DNA chip or microchip.

[0002]

(Problem that this invention tries to solve)

To analyze the DNA (amount of DNA, mutations such as missing DNA, etc.) of a cell or tissue, for example, a micro chip or DNA chip (called a micro chip in the following) with several thousands to 10s of thousands of DNA probes or RNA probes arranged in dots in a predetermined pattern beforehand on a 1 cm^2 glass substrate has been used.

[0003] The method of analyzing DNA which uses this micro chip, uses a known sample of DNA from a certain cell or tissue which is marked with a fluorescent substance. This unknown DNA is placed on a micro chip where DNA probes made from the known sample is arranged in dots. Since DNA itself consists of a double helix, when the DNA probe and unknown DNA are identical, they bond to each other. On the other hand, if they are different, they will not be bonded.

[0004] The unknown DNA which is not bonded on the microchip is removed by washing in a stock-reducing solution, etc. After that, light such as a laser beam is used to irradiate the micro chip, and light from the fluorescent marker on the unknown DNA which has bonded to the DNA probe is detected. By this method, the type or arrangement of the unknown DNA is detected, and DNA analysis is done.

[0005] Formerly, in order to scan the microchip using a laser, the micro chip itself was moved in a two-dimensional pattern. However, this method takes time. Especially, in order to detect the type or arrangement of the unknown DNA, many numbers of micro chips with different DNA probes must be used, and detection takes a lot of time, and analysis efficiency has been extremely poor.

[0006] In addition, another scanning device with the following structure is known. The sample base moves in one dimension, and a lens almost the same size as the micro chip is placed above the sample base. A laser beam is scanned as assembled at each DNA probe using a rotating mirror. Light from the fluorescent marker on the Unknown DNA which has bonded with DNA probe on the micro chip is detected by the light-receiving part.

Since it is necessary to scan all of the microchip in two directions, it is necessary to make the space between the microchip and optical lens wide. Therefore, it is impossible to direct fluorescent light from the fluorescent marker effectively to the optical lens, and sensitivity is poor.

[0007] This invention has been invented in order to solve the above problems with the prior art. Its object is to offer an optical scanning device for biological samples which can perform analysis effectively by remarkably reducing the time required to scan the sample chip.

[0008] Another object of this invention is to offer an optical scanning device for biological samples with excellent sensitivity to light from the fluorescent marker.

[0009] This invention offers an optical scanning device for biological samples which has the following characteristics: An optical scanning device for biological samples 1 scans a sample chip multiple times to locate biological samples that have been marked with a fluorescent substance. The optical scanning device for biological samples in this invention consists of the following: a sample base which makes a roundtrip on the main frame holds the sample chip, a controllable drive mechanism which moves the sample base, an electric motor with a hollow center that rotates around an axis which is perpendicular to the surface of the sample base, a rotation ting arm positioned on the sample base side, a pair of opposing mirrors set up at a 45 degree angle in the radial gap which is perpendicular to the axis of rotation, an object lens set up on the optical axis of one of the mirrors positioned at the end of the arm , a light source with a predetermined beam diameter which illuminates the sample base along the axis of rotation through the pair of mirrors and objective lens, a light-receiving part which receives light from the fluorescent substance generated when the substance is illuminated through the objective lens and the pair of mirrors through the hollow center of rotation. This receiver also outputs electric signals. This optical scanning device for biological samples can detect biological samples marked with a fluorescent substance by scanning the sample chip in an arc on the sample base which moves in a straight line.

[0010]

(Example of practice of this invention)

In the following, one example of practice of this invention is going to be explained using the figures. Figure 1 is a cross section of the optical scanning device for biological samples. Figure 2 is used to explain the optical scanning device.

[0011] The main frame of an optical scanning device for biological samples 1 has a guide axis 5 which runs left and right as shown in the figure. The main frame 3 supports a movable table 7 so that it can make a round trip along this axis. The movable table 7 has a lead screw 9 which is attached to the main frame 3 so that it can be rotated. A movable table 7 is moved at a predetermined speed by a 1st electric motor 11 such as a servo motor or stepper motor connected to the screw 9.

[0012] The 1st electric motor 11 has a position angle detector 11a such as a rotary encoder, etc. In accordance with the 1st electric motor 11, electric signals output from the encoder 11a are used to detect the position of the movable table 7.

[0013] A sample base 13 is attached to the top of this movable table 7. The sample chip 15 such as a microchip or DNA chip which will be optically scanned is temporarily fixed on top of the sample base 13. The sample chip 15 consists of DNA probes (RNA probes) made from a known cell or tissue sample in a dot matrix pattern with a predetermined space between dots. At the same time, unknown DNA (RNA) from cells to be analyzed is marked with a fluorescent substance and hybridized with each DNA probe. In figure 4, the DNA probe is indicated by the symbol O, and the DNA probe where unknown DNA has been hybridized is indicated by double circles.

[0014] The main frame 3 corresponding to the top of the sample base 13 has a 2nd electric motor 17 with a hollow center which extends out in the axial direction attached to the rotating center section 17a such as a servo motor, stepper motor, etc. Its speed can be controlled. The rotor 17a of the 2nd electric motor 17 is supported so that it can be rotated in the motor housing 17d where the stator 17c is attached. A mirror housing 19 which extends in the radial direction is fixed to the ends of the axis of rotation 17a which projects out from the center part of the motor housing 17d.

[0015] The 2nd electric motor 17 has a position detector 17e such as a rotary encoder the same as the 1st electric motor 11. It outputs angle detection signals in accordance with the position of the rotor 17a.

[0016] The mirror housing 19 is long enough to covers the entire width (perpendicular to the moving direction of the sample base 13) even if the rotation diameter is small. It has a hollow center 19a which is connected to the hollow center 17b of the rotor 17a and also extends in the radial direction. A 1st and 2nd mirror 21a, 21b are attached at a 45 degree angle at the ends and in the center of the hollow center 19a. An objective lens 23 is attached to the mirror housing 19 corresponding to reflected axis of the 2nd mirror 21b near the sample base 13.

[0017] The main frame 3 corresponding to the top of the axis rotation 17a has a semi transparent mirror 27 inclined at a 45 degree angle. The main frame 3 has a light source 29 attached on the optical axis of the semi transparent mirror 27 which is perpendicular to the axis of the rotor 17a. The main frame 3 has a light-receiving device 31 attached along the optical axis of the semi transparent mirror 27 which matches the axis of the rotor 17a.

[0018] The light source 29 consists of a laser output device with a wavelength which matches the wavelength of the fluorescent marker in the unknown DNA which has bonded to the DNA probe. It also has a lens which focuses laser light at center of the optical axis of the semi transparent mirror 27 with a predetermined beam diameter (neither is shown in the figure).

[0019] The light-receiving device 31 consists of a light-receiving part (not shown in the figure) such as a photo diode or CCD which outputs electric signals initiated by fluorescent light which passes through the semi-transparent mirror 27 and a band-pass optical filter 31a which passes only the light from the fluorescent marker to the light-receiving part 31a.

[0020] Next, the operation of this optical scanning device for biological samples is going to be explained. Figure 3 shows the scanning trace of the laser beam on the sample chip; figure 4 indicates a sample detection pattern.

[0021] The sample chip 15 is set on the sample base 13, the 1st electric motor 11 is rotation ted, and the movable table 7 moves in the direction of the solid arrow in figure 3.

At the same time, the 2nd electric motor 17 is rotated, and the mirror housing 19 is rotated at a predetermined RPM in a predetermined direction.

[0022] In this condition, when a laser beam with a predetermined wavelength is output from the light source 29, the laser beam is reflected down along the axis of the rotor 17a by the semi transparent mirror 27, and it passes through the hollow center 17b of the rotor 17a. After that, it is reflected in the radial direction which is perpendicular to the axis of the rotor 17a the 1st mirror 21a. Next, the 2nd mirror 21b reflects it down along the axis of the rotor 17a . After that, it passes through the objective lens 23, and it is focused to a predetermined spot diameter on the sample chip 15.

[0023] The laser beam irradiates the top of the sample chip 15 in the pattern shown in figure 3. Along with all the DNA probes arranged in dots on the sample chip 15, the laser beam irradiates the DNA probes where the unknown DNA has been bonded. Next, the fluorescent marker on the unknown DNA emits light when excited by the laser beam. This fluorescent light passes backwards through the light path above, passes through the semi transparent mirror 27, and is received by the light-receiving device 31. This causes the light-receiving part 31a of the light receiving device 31 to output electric signals, and the pattern is stored in the buffer memory of a computer.

[0024] These electrical signals are stored as the rotation angle data output by the encoder 17e of the 2nd electric motor 17 and the position data of sample base 13 output from the encoder 11a.

[0025] The computer converts these two angular coordinated to X-Y data based data which has been programmed already. Next, as shown in figure 4, the pattern of unknown DNA on the sample chip 15 is displayed.

[0026] The scan time of the sample chip 15 is determined by the A/D processing speed of the computer, detection points of the fluorescent light, size of the sample chip 15, displacement of the sample chip 15, and RPM of the 2nd electric motor 17, etc.

[0027] This example of practice can reduce scanning time a great deal compared to conventional two axis scanning methods. Detection of the sample chip 15 can be done effectively. Furthermore, since the sample chip 15 is scanned through an objective lens 23 which is close to sample chip 15, fluorescent light from sample chip 15 is captured by the objective lens 23 effectively, and fluorescent light can be detected with high sensitivity.

[0028]

(Effects of this invention)

This invention offers an optical scanning device for biological samples which can perform analysis effectively by reducing the time required to scan the sample chip remarkably. It offers an optical scanning device for biological samples with excellent sensitivity to light from the fluorescent marker in the biological sample. It can also increase accuracy.

(Simple explanation of figures)

Figure 1: cross section of the optical scanning device for biological samples

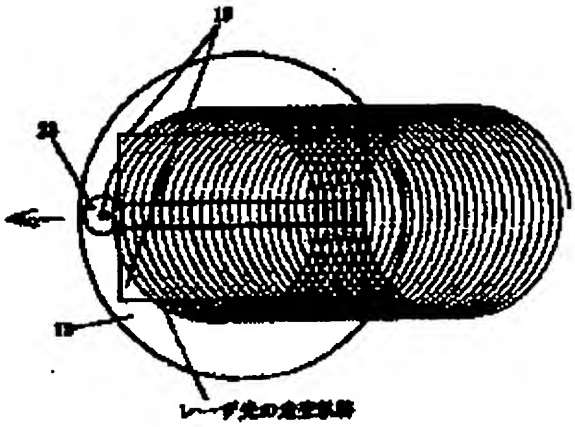
Figure 2: figure used to explain the scanning device for biological samples

Figure 3: scanning trace of the laser beam on the sample chip

Figure 4: detection pattern example.

(Explanation of symbols in figures)
1: biological sample optical scanning device
3: main frame
11: 1st electric motor
13: sample base
15: sample chip
17: 2nd electric motor
17a: rotor
17b: hollow center
23: objective lens
29: light source
29: semi transparent mirror
31: light receiving device

【図3】



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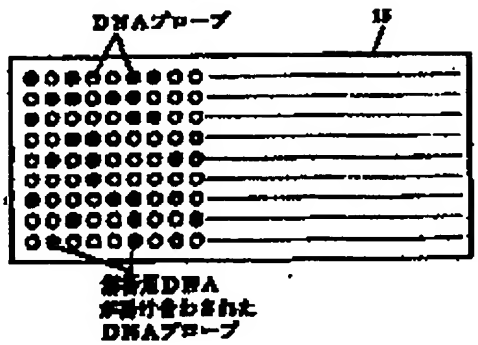
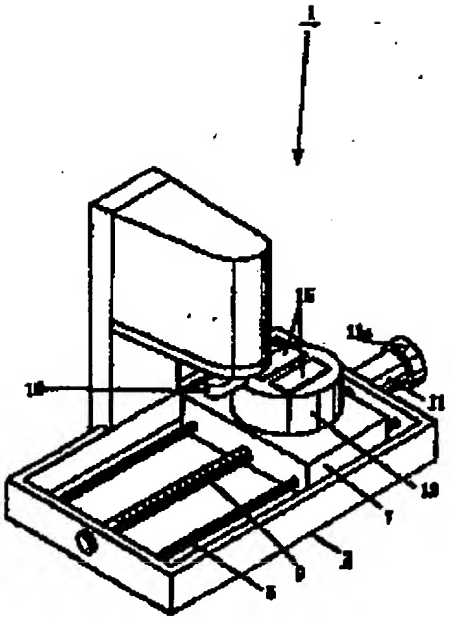


【図1】



【図2】